Role of Surgery for N2 disease

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Disclosures

- Consultancy / Advisory Board
  - Stratagen, Abbott Molecular, Glaxo Smith Klein, Pfizer, Norvatis, Covidien, Ethicon

- Educational presentations / speaker
  - Roche, Imedex, Glaxo Smith Klein, Lily, Pfizer, Medela, Boehringer Ingelheim, Ethicon

- Travel, accommodation and course fees
  - Covidien, Medela

- Research funding
  - ScreenCell®, Meleda

- Other
  - Founder of Informative Genomics (blood based molecular diagnostics laboratory)
  - Director of the BUPA Cromwell Lung Cancer Screening Programme
  - Chief Investigator for MARS 2 – surgery versus no surgery for mesothelioma
  - Chief Investigator for VIOLET – VATS versus thoracotomy for lung cancer
Clinical surgeon

- Consultant Thoracic Surgeon, Royal Brompton Hospital, London, UK
  - National Centre for Thoracic Surgery
  - Support international referrals
    - Neuroendocrine tumours
  - UK clinical service provision
  - Train UK and international surgeons
Clinical academic

- Reader in Thoracic Surgery, Imperial College, London, UK
  - Undergraduate medical education
  - Research supervision PhD

- Qualified Medical Statistician
  - MSc tutor at University of London
Academic portfolio

- Book and chapter author
- Research
  - Translational science
    - Patents (microfluidics and blood based mutation testing)
  - Statistical methodology
  - Healthcare evaluation
  - Outcomes in thoracic surgery
- UK lead thoracic surgery research
Chief Investigator for Thoracic Surgery Trials

- MARS 2 – multicentre RCT of surgery (versus no surgery) for malignant mesothelioma
  - CRUK funded trial (£142,000)

- VIOLET – Keyhole versus open surgery for lung cancer
  - NIHR HTA funded trial (£1,700,000)
National and international guidelines

Guidelines on the Radical Management of Patients with Lung Cancer

Eric Lim, David Baldwin, Michael Beckles, John Duffy, James Entwisle, Corinne Faivre-Finn, Keith Kerr, Alistair Macfie, Jim McGuigan, Simon Padley, Sanjay Popat, Nicholas Screaton, Michael Sne, David Waller, Chris Warburton, Thida Win

On behalf of the British Thoracic Society and Society for Cardiothoracic Surgery in Great Britain and Ireland Lung Cancer Guideline Group: a sub-group of the British Thoracic Society Standards of Care Committee

2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up

J. Vansteenkiste¹, L. Crinò², C. Dooms¹, J. Y. Douillard³, C. Faivre-Finn⁴, E. Lim⁵, G. Rocco⁶, S. Senan⁷, P. Van Schil⁸, G. Veronesi⁹, R. Stahel¹⁰, S. Peters¹¹, E. Felip¹² & Panel Members†

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. Vansteenkiste¹, D. De Ruyscher², W. E. E. Eberhardt³, E. Lim⁴, S. Senan⁵, E. Felip⁶ & S. Peters⁷, on behalf of the ESMO Guidelines Working Group*

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin¹*, E. Baudin², P. Ferolla³, P. Filosso⁴, M. Garcia-Yuste⁵, E. Lim⁶, K. Oberg⁷, G. Pelosi⁸, A. Perren⁹, R. E. Rossi¹,¹⁰ & W. D. Travis¹¹ the ENETS consensus conference participants†
Programme for today

- Staging for N2 disease
- Evidence for surgical multi-modality treatment of N2 disease
- Re-staging after induction treatment of N2 disease
- Discussion on lack of uptake for surgery for N2 disease
1. What’s the fastest way out of King’s Cross in London?

1. London tube
2. London bus
3. London black cab
Depends where you want to go?!! Paris via Eurostar
Before how to get there, need to know where you want to go?
The diagnosis and treatment of lung cancer (update)
1. Before we decide method of investigation, we first decide on purpose.
2. What is the main purpose of invasive mediastinal staging?

1. For completeness of staging
2. Because guidelines say so
3. To screen patients with cN2 out from surgery
2. Purpose of invasive mediastinal staging to **exclude** patients with N2 disease for surgery
This presentation contains graphic plots of statistical nature some may find disturbing
3. Which statement is true?

1. Treatment A is likely better
2. Treatments A & B are similar
3. Treatment B is likely better

P = 0.954

NOTE: Weights are from random effects analysis
3. Which statement is true?

1. Treatment A is likely better
2. Treatments A & B are similar
3. Treatment B is likely better

P=0.068

NOTE: Weights are from random effects analysis
Randomized study of chemotherapy and surgery versus radiotherapy for stage IIIA non-small-cell lung cancer: a National Cancer Institute of Canada Clinical Trials Group Study.

Shepherd FA, Johnston MR, Payne D, Burkes R, Deslauriers J, Cormier Y, de Bedoya LD, Ottaway J, James K, Zee B

Thirty-one patients with stage IIIA (N2) non-small-cell lung cancer were randomized to receive radiotherapy alone or chemotherapy with cisplatin and vinblastine followed by surgery. Response rates to induction chemotherapy and radiotherapy were 50% and 53.3% respectively. Complete surgical resection was possible for 62.5% of patients. Median survival times were 16.2 and 18.7 months for radiotherapy alone and chemotherapy-surgery respectively (P = NS), with no long-term improvement in survival seen with combined-modality treatment.

Br J Cancer. 1998 Sep;78(5):683-5
PHASE III STUDY COMPARING CHEMOTHERAPY AND RADIOTHERAPY WITH PREOPERATIVE CHEMOTHERAPY AND SURGICAL RESECTION IN PATIENTS WITH NON–SMALL-CELL LUNG CANCER WITH SPREAD TO MEDIASTINAL LYMPH NODES (N2); FINAL REPORT OF RTOG 89-01

David W. Johnstone, M.D.,* Roger W. Byhardt, M.D.,† David Ettenger, M.D.,‡ and Charles B. Scott, Ph.D.§

The overall progression-free survival rate was 53% at 1 year and 17% at 3 years. The median progression-free survival was 14 months. No difference in the 1-year survival rate (70% vs. 66%) or median survival time (19.4 vs. 17.4 months) between the surgery and RT arms. The median survival in the patients receiving induction chemotherapy only was 8.9 months. Mitomycin-C had no impact on survival ($p = 0.75$). No statistically significant difference was noted in the time to local failure between the surgical and RT arms.

Conclusion: The patient accrual to this trial made its results inconclusive, but several observations are notable. In this trial, histologic confirmation of N2 disease in the surgical and nonsurgical arms eliminated the usual biases from clinical staging. In this setting, local control and survival were essentially equal between the surgical and RT arms. The 3- and 5-year survival rates of nonsurgical therapy were comparable to published surgical trials of N2 disease. © 2002 Elsevier Science Inc.
A randomised controlled trial of pre-operative chemotherapy followed, if feasible, by resection versus radiotherapy in patients with inoperable stage T3, N1, M0 or T1-3, N2, M0 non-small cell lung cancer

Richard J. Stephens\textsuperscript{a,*}, David J. Girling\textsuperscript{a}, Penelope Hopwood\textsuperscript{b}, Nicholas Thatcher\textsuperscript{b}

on behalf of the Medical Research Council Lung Cancer Working Party

Overall survival was similar in the two groups (HR 0.91, 95% CI 0.49–1.72, \( p = 0.78 \)). Median survival was 11.2 and 13.8 months, 1-year survival 43 and 54%, and 2-year survival 16 and 15% for the RT and CT-S groups, respectively.
Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non-Small-Cell Lung Cancer


In selected patients with pathologically proven stage IIIA-N2 NSCLC and a response to induction chemotherapy, surgical resection did not improve overall or progression-free survival compared with radiotherapy. In view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment for these patients.
Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyan Chen, Robert B Livingston, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, William T Sause, James D Cox

Interpretation Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with stage IIIA(N2) non-small-cell lung cancer.
Surgery for NSCLC stages T1-3N2M0 having preoperative pathologically verified N2 involvement: A prospective randomized multinational phase III trial by the Nordic Thoracic Oncology Group.

Jens Benn Sorensen, Jesper Ravn, Han Kristian Pilegaard, Torben Palshof, Stein Sundstrom, Bengt Bergman, Jan Nyrop Jakobsen, Ulf Aasebø, Olaf Olsen, Peter Meldgaard, Bente Thornfeldt Soerensen, Erik Jakobsen, Per Jonsson, Marianne Ryberg, Jarmo Salo, Rune Haverstad, Henrik Riska; Department of Oncology, Finsen Centre, National University Hospital, Copenhagen, Denmark; Department of Thoracic Surgery, National University Hospital, Copenhagen, Denmark; Department of Thoracic Surgery, Skejby Hospital, Aarhus, Denmark; Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; Sct. Olafs Hospital, Trondheim, Norway; Sahlgrenska University Hospital, Göteborg, Sweden; National University Hospital, Copenhagen, Denmark; University of Tromsø, Tromsø, Norway; Department of Oncology, Odense University Hospital, Odense, Denmark; Aarhus University Hospital, Aarhus, Denmark; Vejle Hospital, Vejle, Denmark; Thoracic Surgery, Odense University Hospital, Odense, Denmark; Thoracic Surgery, Lund University Hospital, Lund, Sweden; Herlev University Hospital, Herlev, Denmark; Thoracic Surgery, Helsinki University Hospital, Helsinki, Finland; Thoracic Surgery, Haukeland University Hospital, Bergen, Norway; Helsinki University Hospital, Helsinki, Finland

**Background:** Surgery is not generally considered standard of care in preoperative pathological verified spread to N2 mediastinal lymph nodes in NSCLC. **Methods:** Previously untreated histologically verified NSCLC stages T1-3N2M0 were randomized to reg. A (Paclitaxel 225 mg/m2 + Carboplatin AUC6 day 1 q 3 wks for 3 courses, followed by surgery with ipsilateral mediastinal lymph node sampling followed by radiotherapy 2Gy x 30 fractions, 5F/W) or reg. B: same as A without surgery (sequential chemo-radiotherapy). 406 pts were needed to detect a 10% 5-year survival increase with 80% power and type 1-error of 5%. The study was approved by ethical committees. Pts gave informed consent. **Results:** 170 pts were randomized to A and 171 to B from 1998-2009 when study closed due to concomitant chemo-radiotherapy becoming standard instead of sequential treatment. Median age was 61 years (range 33-76 yrs), 59% were males, 43% had performance status 0. Stages T1N2M0, T2N2M0, and T3N2M0 occurred in 19%, 60%, and 21%, respectively. Adenocarcinoma (ADC) and squamous cell carcinoma occurred in 50% and 29%, respectively. In reg. A, surgery was possible in 132 out of 170 pts (78%), 121 pts (71%) had complete resection while 11 pts (6%) had incomplete resection. Pathological-surgical stage pT0 occurred in 4%. Median progression free survival (PFS), OS and 5-years survival rate were 10 mths, 17 mths, and 20% for A (+ surgery) compared to 8 mths (p=0.144), 15 mths (p=0.172), and 16% (p=0.310) for B, respectively. ADC pts had better OS in A than in B (HR 0.60; p=0.002), and 5-year survivals 20% and 7% (p=0.017) respectively. Stage T1N2 had better OS in A than in B (HR 0.47; p=0.010), 5-year survivals 36% and 17%. **Conclusions:** There were no statistical overall significant advantage for surgery in addition to chemo-radiotherapy (A) compared to chemo-radiotherapy alone (B) but ADC pts and pts with T1N2 had significantly improved OS and 5-year survival rates in the surgery arm. Current standard treatment for T1-3N2M0 NSCLC is concomitant chemo-radiotherapy which was not used in this study, hence conclusions should be further tested with use of such treatment as reference arm.

J Clin Oncol 31, 2013 (suppl; abstr 7504)
Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials

P J McElnay, A Choong, E Jordan, F Song, E Lim

HR 1.01 (0.82 to 1.23; $P=0.954$)

HR 0.87 (0.75 to 1.01; $P=0.068$)

HR 0.92 (0.81 to 1.03; $P=0.157$)
Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non–Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)

Wilfried Ernst Erich Eberhardt, Christoph Pöttgen, Thomas Christoph Gauler, Godehard Friedel, Stefanie Veit, Vanessa Heinrich, Stefan Welter, Wilfried Budach, Werner Spengler, Martin Kimmich, Berthold Fischer, Heinz Schmidberger, Dirk De Ruyscher, Claus Belka, Sebastian Cordes, Rodrigo Hepp, Diana Lütke-Brintrup, Nils Lehmann, Martin Schuler, Karl-Heinz Jöckel, Georgios Stamatis, and Martin Stuschke

Conclusion
The 5-year OS and PFS rates in randomly assigned patients with resectable stage III non–small-cell lung cancer were excellent with both treatments. Both are acceptable strategies for this good-prognosis group.
3. Systematic review of RCTs of cN2 disease show:

a. surgery as bimodality treatment has same survival as chemo-radiotherapy
b. surgery as tri-modality treatment has better survival than chemo-radiotherapy
Role of surgery for cN2 disease

- If you accept the role of surgery for cN2 disease
  - Based on level 1a evidence (systematic reviews of 6 RCTs)
- You can accept test performance of PET/CT for mediastinal node staging
- You do not need to screen patients out with invasive mediastinal staging
4. No need to screen patients out with invasive mediastinal staging:

   Eliminate complications of invasive staging (patient thanks you)  
   Reduce cost of biopsy (hospital and country thanks you)  
   Reduce the time to definitive treatment (society thanks you)
Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyau Chen, Robert B Livingston, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, William T Sause, James D Cox

N=202

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<table>
<thead>
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<tbody>
<tr>
<td>Pathological N0 (n=76)</td>
<td>41%</td>
</tr>
<tr>
<td>Pathological N1-3, unknown (n=88)</td>
<td>24%</td>
</tr>
<tr>
<td>No surgery (n=38)</td>
<td>8%</td>
</tr>
</tbody>
</table>

5 year survival
Summary

1. Before we decide method of investigation we first decide on purpose

2. Purpose of invasive mediastinal staging to exclude patients with N2 disease for surgery

3. There is level 1a evidence in support of surgery for clinical N2 disease
   a) Not fixed N2
   b) Not bulky disease

4. Therefore no need to screen patients out and we will improve clinical care
   a) Reduce cost of biopsy
   b) Eliminate complications of invasive staging
   c) Reduce the time to definitive treatment
Why isn’t surgery offered more for N2 disease?
Barriers to the uptake of evidence from systematic reviews and meta-analyses: a systematic review of decision makers’ perceptions

John Wallace,1 Bosah Nwosu,2 Mike Clarke3

<table>
<thead>
<tr>
<th>Surveys</th>
<th>Number of barriers addressed by each study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al (2001)</td>
<td>4: Lack of access, awareness, use and training</td>
</tr>
<tr>
<td>Hanson et al (2004)</td>
<td>2: Lack of trust and training</td>
</tr>
<tr>
<td>Poolman et al (2007)</td>
<td>2: Lack of understanding, use</td>
</tr>
<tr>
<td>Dahm et al (2009)</td>
<td>3: Lack of awareness, use and understanding,</td>
</tr>
<tr>
<td>McAllister et al (1999)</td>
<td>1: Lack of use</td>
</tr>
<tr>
<td>Wilson et al (2001)</td>
<td>1: Lack of access</td>
</tr>
<tr>
<td>Ward and Young (2001)</td>
<td>3: Lack of access, understanding and usefulness</td>
</tr>
<tr>
<td>Kerse et al (2001)</td>
<td>3: Lack of access, awareness and use</td>
</tr>
<tr>
<td>Bennett et al (2001)</td>
<td>1: Lack of confidence</td>
</tr>
<tr>
<td>Young and Ward (1999)</td>
<td>3: Lack of awareness, access and use</td>
</tr>
<tr>
<td>Paterson-Brown (1993)</td>
<td>3: Lack of awareness, availability and need</td>
</tr>
<tr>
<td>Prescott et al (1999)</td>
<td>2: Lack of use and awareness</td>
</tr>
<tr>
<td>Cliska et al (1999)</td>
<td>4: Lack of awareness, use, policy climate and resources</td>
</tr>
<tr>
<td>Olatunbosun et al (1998)</td>
<td>1: Lack of access</td>
</tr>
<tr>
<td>Gawani et al (2009)</td>
<td>2: Lack of use and usefulness</td>
</tr>
<tr>
<td>Wilson et al (2003)</td>
<td>4: Lack of access, awareness, use and training</td>
</tr>
<tr>
<td>Carey and Hall, (1999)</td>
<td>1: Access</td>
</tr>
<tr>
<td>Lawrie et al (2000)</td>
<td>1: Ability to search</td>
</tr>
<tr>
<td>Hyde et al (1995)</td>
<td>1: Ability to search</td>
</tr>
<tr>
<td>Martis et al (2008)</td>
<td>5: Lack of access, awareness, use, usefulness and training</td>
</tr>
<tr>
<td>Qualitative studies</td>
<td></td>
</tr>
<tr>
<td>Dobbins et al (2007)</td>
<td>4: Lack of relevance, implications, implementation strategies and understanding of the information needs of the target audience</td>
</tr>
<tr>
<td>Wilson et al (2001)</td>
<td>7: Limited range, access, focus, use, up-datedness, promotion and time</td>
</tr>
</tbody>
</table>
Thoracic surgical oncology

- Is not really an evidenced based field
- Thoracic oncology community not used to evidence
- Simply because there is hardly any evidence
Thoracic Surgeons

- **Internal considerations**
  - Don’t know the evidence
  - Don’t trust the interpretation of the evidence

- **External considerations**
  - Don’t want to be labelled as a maverick (weaponised term)
  - Are concerned on litigation and accusations of malpractice
Oncologists

- Outnumber surgeons
- More research orientated than surgeons
- Know the evidence
- Design the trials, run the trials, report the trials
- Very strong presence in many guidelines
- Backed by multi-billion dollar companies
- Fiercely protective of their speciality
- May be the referring clinicians (control patient flow)
Doctor knows best
Patient knows best

No more tests → Decision → Patient → Treatment

Do we need any more tests?
We should integrate clinical expertise, patient values, and the best research evidence into the decision making process for patient care.

Evidence Based Medicine, David Sackett, 2002
Clear, accurate information about the risks of any proposed investigation or treatment, presented in a way patients can understand, can help them make informed decisions. The amount of information about risk that you should share with patients will depend on the individual patient and what they want or need to know. Your discussions with patients should focus on their individual situation and the risk to them.

You should do your best to understand the patient’s views and preferences about any proposed investigation or treatment, and the adverse outcomes they are most concerned about. You must not make assumptions about a patient’s understanding of risk or the importance they attach to different outcomes. You should discuss these issues with your patient.²

The patient weighs up the potential benefits, risks and burdens of the various options as well as any non-clinical issues that are relevant to them. The patient decides whether to accept any of the options and, if so, which one. They also have the right to accept or refuse an option for a reason that may seem irrational to the doctor, or for no reason at all.²
The landmark decision of the Supreme Court in *Montgomery v Lanarkshire Health Board* has confirmed that a patient’s right to self-determination in treatment decisions triumphs over medical paternalism.

The practical effect is that patients with full mental capacity must be properly advised about their treatment options and the risks associated with each option so that they can make informed decisions when giving or withholding consent to treatment.

In other words, the principles of shared decision-making must become the norm.

Thank you!


Invasive mediastinal staging is irrelevant for PET/CT positive N2 lung cancer if the primary tumour and ipsilateral lymph nodes are resectable.

PMID: 26380888
Preoperative versus Postoperative Chemotherapy in Patients with Resectable Non-small Cell Lung Cancer

Systematic Review and Indirect Comparison Meta-Analysis of Randomized Trials

Eric Lim, MB, ChB, MD, MSc, FRCS,* Grace Harris, MBBS,* Amit Patel, MB, ChB, MRCS,* Iki Adachi, MD,* Lyn Edmonds, MCLIP,† and Fujian Song, BMed, MMed, PhD‡

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-yr Survival Reported</th>
<th>Postoperative Chemotherapy</th>
<th>Preoperative Chemotherapy</th>
<th>Difference (Postoperative versus Preoperative)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
<td>Expected</td>
</tr>
<tr>
<td>IA</td>
<td>73</td>
<td>78.4</td>
<td>76.4</td>
<td>80.3</td>
</tr>
<tr>
<td>IB</td>
<td>54</td>
<td>63.2</td>
<td>59.8</td>
<td>66.4</td>
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<tr>
<td>IIA</td>
<td>48</td>
<td>58.5</td>
<td>54.6</td>
<td>62.0</td>
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<tr>
<td>IIB</td>
<td>38</td>
<td>50.5</td>
<td>45.9</td>
<td>54.7</td>
</tr>
<tr>
<td>IIIA</td>
<td>25</td>
<td>40.1</td>
<td>34.5</td>
<td>45.3</td>
</tr>
<tr>
<td>IIIB</td>
<td>19</td>
<td>35.3</td>
<td>29.3</td>
<td>40.9</td>
</tr>
<tr>
<td>IV</td>
<td>21</td>
<td>36.9</td>
<td>31.0</td>
<td>42.3</td>
</tr>
</tbody>
</table>

All numbers are given as a percentage. Bold font indicates the tumour stage for which the data is most applicable.